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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/175,683	10/20/98	CHEN L	107.637.121-

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EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/175,683	Applicant(s) Chen
	Examiner Richard Schnizer	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-26 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-26 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5,9

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

The instant application claims priority to two provisional applications. The first sentence of the specification should be amended to reflect this.

Specification

The specification should be reviewed for spelling and grammatical errors. See for example page 10, line 20, and page 11, line 16.

Claim Objections

All claims are objected to because of a variety of informalities: For example: The words "AT" and "containing" in claims 1, 6, and 10 should be joined by a hyphen; the word "motifs" in claims 2 and 23 should be changed to "motif"; the words "gene" and coding" in claim 2 should be joined by a hyphen; the words "protein" and "specific" in claims 3, 4 and 10 should be joined by a

hyphen; the words "AT" and "content" should be joined by a hyphen; and the words "mammary" and "specific" in should be joined by a hyphen. All grammatical errors in the claims should be corrected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-26 are indefinite because they recite "the gene", or "the known gene", or "the natural gene" without antecedent basis.

Claims 1-12, 22, 24, and 25 are indefinite because they recite a "known nucleic acid" and the specification does not define what is encompassed by the genus of "known" nucleic acids. The definition of this genus is dependent on the knowledge of indiviuals and/or the information stored in databases. It is unclear who it is that must be familiar with the nucleic acid, or in what database the information must deposited. Furthermore, because the genus of known nucleic acids changes with time, and it is unclear at what time the nucleic acid must be known in order to meet the claim. Deletion of the term "known" is suggested.

Claims 2, 7, 10, and 11 are indefinite because they recite "the replaced codon" without antecedent basis. These claims are drawn to the replacement of an mRNA instability motif with a codon. The specification teaches only one instability motif, and it consists of 5 nucleotides. It is noted that replacement of 5 nucleotides with a codon will result in a frameshift.

Claims 2, 3 and 7 are indefinite because they recite a "nucleic acid of a parasite protein". Proteins do not have nucleic acids. It is suggested that the word "of" be replaced by the word "encoding".

Claims 3-12, 17-21, and 26 are indefinite because they recite " a milk protein-specific codon" or "a mammary-specific codon". These terms are not defined in the specification. In general, the terms milk protein-specific or mammary-specific would be understood to refer to items which are found only in milk or mammary tissue. One of skill in the art appreciates that there are no codons which are used exclusively in milk or mammary tissue.

Claims 4, 5, 8, and 9 are unclear because the phrase "the known gene encoding is lowered by" makes no sense. It is suggested that the word "encoding" should be deleted. These claims are also drawn to lowering the "the overall AT content of the known gene" by replacement with "a milk specific-codon". It is not clear how many codons one should employ in lowering the overall AT content of the gene. For example, one could lower the AT-content by replacement of all codons, excepting the start and stop codons, with a single codon which lacks A and T.

Claims 8 and 9 are indefinite because they recite "the method" of claim 5. Claim 5 recites no method.

Claims 8, 10 and 11 are indefinite because they recite "said protein" without antecedent basis.

Claims 10, 11, 22, 24, and 25 are indefinite because they recite "the AT -rich content" without antecedent basis. Deletion of the word "rich" is suggested.

Claim 12 is indefinite because it identifies malaria as a parasite. Malaria is a disease. *Plasmodium falciparum* is a parasite.

Claims 12 and 14-22 are indefinite because they recite the term "specifically homologous". This term is defined at page 8, line 6-15 of the specification, but the definition is non-limiting. "Specifically homologous" sequences are said to "specifically hybridize" to an exact complement of a given sequence. A sequence "specifically hybridizes" if it hybridizes either "in the body", or under "approximate physiological conditions with respect to ionic strength", or under "stringent conditions". These definitions are indefinite for several reasons. First, the type of body in which hybridization should occur is not disclosed. Different bodies have different body temperatures. For example, smaller mammals tend to have higher body temperatures than larger mammals, and the temperature of non-homeothermic bodies varies to some extent with ambient temperature. Second "approximate physiological conditions with respect to ionic strength" will also vary with the physiology in question. Applicant has not disclosed any specific physiology, and offers only a non-limiting example of NaCl and $MgCl_2$ concentrations. Finally, "stringent conditions" are not defined and only a non-limiting example is given. The definition of "stringency" as it pertains to hybridization conditions is subject to interpretation and is different from laboratory to laboratory.

Therefore, without a clear and explicit recitation of what conditions are meant to be included by "in the body", "approximate physiological conditions with respect to ionic strength", and "stringent", the meaning of "specifically homologous" is unclear, and a skilled artisan would not be reasonably apprised of the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 11, 12, 14-16, and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by random hexameric nucleic acids, product $pd(N)_6$ in the 1995 Pharmacia Biotech catalogue, page 277.

Claims 1-5, 11, 12, 14-16, and 22-24 are product by process claims in which the process by which the product is produced carries no patentable weight. Th.e product is a nucleic acid which is a fragment of a modified known parasite protein. The fragment may be of any length. The 1995 Pharmacia Biotech catalogue teaches random hexamer nucleic acids. This mixture of nucleic acids comprises all possible combinations of nucleic acid hexamers. Therefore, all two-codon fragments of any nucleic acid are represented in this collection of random hexamers. Thus product $pd(N)_6$ anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12, 14-19 and 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dziegiel et al (US Patent 5,231,168, issued 7/21/93), Holder et al (Nature 317(6034): 270-273, 9/1985), Seed et al (US Patent 5,795,737, filed 9/2/95), Akashi et al (Blood 83(11): 3182-3187, 6/1994), Bosch et al (US Patent 5,736,131, filed 9/1/94), and Wang et al (J. Biol. Chem. 264: 21116-21121, 1989).

Dziegiel teaches an expression vector comprising a nucleic acid encoding an antigen of Plasmodium falciparum. See abstract. The expression vector may be used in mammalian cells. See column 18, lines 54-65. The GC content of the nucleic acid is about 30%. See column 16, lines 40-43. Prior to use of the expression vector, the nucleic acid may be modified by silent nucleotide substitutions which favor the codon usage of the organism in which the nucleic acid will be expressed. See column 20, line 66 to column 21, line 7; and column 21, lines 36-40. The nucleic acid may also be used as a vaccine, particularly as part of a virus. See column 25, lines 32-66. Dziegiel does not teach reducing the AT-content of the nucleic acid, the removal of mRNA instability motifs, or the introduction of codons found in milk- or mammary-specific proteins.

Holder teaches the primary structure of the precursor to the three major surface antigens of *Plasmodium falciparum* merozoites. This sequence is 72.8% identical to SEQ ID NO:1 and 72% identical to SEQ ID NO:8, and can be considered specifically homologous to both SEQ ID NO:1 and SEQ ID NO:8. The coding region of this sequence comprises AUUUA motifs identical to those which have been found in 3'-untranslated regions of mRNAs. These sequences are known in the art, and identified in the specification, as mRNA destabilizing sequences. Holder also teaches that these antigens may be useful for immunization against *P. falciparum*. See abstract, and Fig. 2, page 272. Also see enclosed sequence alignments. Holder does not teach reducing the AT-content of the nucleic acid, the removal of mRNA instability motifs, or the introduction of codons found in milk- or mammary-specific proteins.

Seed teaches that codon optimization may be used to increase the expression of foreign genes in mammalian cells. See column 1, lines 8-10; and column 2 lines 7-11. Preferred codons are always those with the highest possible GC content. See lines 33-37, and Table 1, bridging columns 7 and 8. Synthetic genes comprising preferred codons can be expressed mammalian culture systems in amounts in excess of 110% of the amount that the natural gene is expressed in the same systems. See column 2, lines 16-22.

Bosch teaches removal of mRNA instability motifs from nucleic acids which are to be expressed in heterologous hosts. Bosch also teaches that codon optimization is advisable. See column 4, lines 12-21.

Akashi teaches that the function of AUUUA mRNA destabilization motifs is not restricted by their location within the mRNA. These motifs need not be located in the 3'-untranslated region of mRNAs, and are capable of destabilizing mRNAs even when located within the coding region. See abstract, and Fig. 1.

Wang teaches a milk-specific protein expressed in mammary tissue which comprises GC-rich codons. See Figure 2, column 1, page 21118, see particularly glycine codons at positions -11 and 18.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the nucleotide sequences of Dziegiel or Holden by decreasing their AT-content and removing mRNA destabilization motifs. One would have been motivated to do so because Seed teaches that, of all the codons encoding a given amino acid, the preferred codon for expression in mammalian cells is the one with the highest GC-content. One would have been motivated to express the nucleic acid in mammalian cells because Dziegiel teaches the use of a nucleic acid encoding a malarial antigen as a DNA vaccine. One would have been motivated to remove mRNA-destabilizing motifs from the coding region of the nucleic acids because Akashi teaches that these sequences are active in the context of the coding region, and because Bosch suggests that mRNA-destabilizing motifs should be removed from sequences to be expressed in heterologous hosts.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute codons found in milk- or mammary-specific proteins for those found in the nucleic

acids of Dziegiel or Holden. One would have been motivated to do so because Seed teaches that GC-rich codons are preferred in mammalian cells. For example, glycine can be encoded by GGA, GGT, GGG, and GGC. The preferred codon is GGC, followed by GGG. See Table 1, column 7. The sequence of Wang comprises GGC glycine codons at positions -11 and 18. Thus, if one were to substitute a GC codon for a GGA codon as taught by Seed, one would be using a codon found in a milk- or mammary-specific protein.

Thus the invention as a whole was *prima facie* obvious.

Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dziegiel, Holder, Seed, Akashi, Bosch, and Wang as applied to claims 1-12, 14-19 and 22-26 above, and further in view of Bleck et al (US Patent 5,530,177, issued 6/1996).

The teachings of Dziegiel, Holder, Seed, Akashi, Bosch, and Wang are discussed in the previous rejection. Briefly, these references can be combined to teach an expression vector encoding a modified nucleic acid specifically homologous to either SEQ ID NO:1 or SEQ ID NO:8.

These references do not teach a transgenic animal whose germ line comprises the nucleic acid, or an expression vector wherein a promoter directs mammary gland expression of the protein encoded by the nucleic acid.

Bleck teaches a method of expressing recombinant proteins in the milk of female mammals. The method comprises operatively linking an α-lactalbumin promoter to an exogenous

gene sequence, and generating a transgenic animal which comprises the hybrid gene. The α-lactalbumin promoter directs expression in mammary tissue. The expressed protein is secreted into the mammal's milk, from which it can be purified. See column 2, lines 34-46. The transgenic animals may comprise the expression construct in their germ line cells. See column 9, line 49 to column 10, line 31, especially column 10 lines 29-31.

It would have been obvious to one of ordinary skill in the art at the time of the invention to link the nucleic acid of Dziegiel, Holder, Seed, Akashi, Bosch, and Wang to the α-lactalbumin promoter of Bleck, and to subsequently construct a transgenic mammal comprising the expression construct. This would allow one to produce and purify the antigen encoded by the nucleic acid. One would have been motivated to so because it was well known in the art at the time of the invention that the nucleic acid encoded a major surface antigen of Plasmodium falciparum merozoites, and that such an antigen could be useful in the preparation of a vaccine. See Holder, abstract.

Thus the invention as a whole was *prima facie* obvious.

Claims 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dziegiel, Holder, Seed, Akashi, Bosch, and Wang as applied to claims 1-12, 14-19 and 22-26 above, and further in view of Robinson et al (US Patent 5,643,578, filed 1//2793).

The teachings of Dziegiel, Holder, Seed, Akashi, Bosch, and Wang are discussed in the previous rejection. Briefly, these references can be combined to teach a modified nucleic acid of a

parasite or a virus in which the modification is conservative replacement of naturally occurring codons in order to decrease AT-content and remove mRNA instability motifs. See Seed, column 2, lines 7-11 for reference to viral nucleic acids. These references do not teach a modified bacterial nucleic acid.

Robinson teaches methods of genetic immunization against bacteria, viruses, and malarial parasites. See abstract; and column 3, lines 20-35. Vaccines consist of a transcription unit comprising promoter elements and antigen-encoding DNA. See column 2, lines 55-61.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the bacterial nucleic acid sequences of Robinson by reducing AT-content and eliminating mRNA destabilization motifs as taught by the combination of Dziegiel, Holder, Seed, Akashi, Bosch, and Wang. One would have been motivated to do so because Seed teaches that GC-rich codons are preferred in mammalian cells, because Bosch suggests removal of mRNA destabilization motifs from nucleic acids which will be expressed in heterologous hosts, and because Robinson suggests expressing bacterial sequences in mammalian cells.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday-Friday from 7:30 to 4:00 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at 703-308-2035. The FAX phone number for art unit 1632 is 703-308-0294.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800